PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Dose Optimization and Scarce Resource Allocation: Two Sides of the Same Coin
AUTHORS	Strohbehn, Garth; Persad, Govind; Parker, William; Murthy, Srinivas

VERSION 1 – REVIEW

REVIEWER	Matrajt, Laura Fred Hutchinson Cancer Research Center Vaccine and Infectious Disease Division
REVIEW RETURNED	13-Jun-2022

GENERAL COMMENTS	In the manuscript entitled “Dose Optimization and Scarce Resource Allocation: Two sides of the same coin”, Strohbehn et al. discuss the use of dose optimization during a pandemic as a way to stretch the available supply of a scarce resource (a vaccine for example). The manuscript is well written and the points made are clear and well documented. My only comments are: 1) the manuscript can be strengthen if the authors add to their manuscript the fact that mathematical models of fractional dosing (for COVID and for other infectious diseases like cholera or flu) have shown that providing a lower dose (with potentially a lower efficacy) to more people can indeed be the optimal use of resources when the goal is to minimize overall deaths or infections. However, caution needs to be taken as there is a threshold in the efficacy: if lowering the dose reduces the efficacy too much, then fractional dosing becomes ineffective. 2) I also suggest the authors add this citation https://www.nature.com/articles/s41591-021-01440-4 As this paper has already dealt with this problem before.

REVIEWER	Gray, Andy L University of Kwazulu-Natal, Discipline of Pharmaceutical Sciences I have no specific conflicts of interest. I serve on the South African National Essential Medicines List Ministerial Advisory Committee on COVID-19 Therapeutics as well as three advisory committees at the South African Health Products Regulatory Authority.
REVIEW RETURNED	13-Jul-2022

GENERAL COMMENTS	The authors have presented a thought-provoking and well-reasoned commentary, highlighting a critical issue from a novel perspective. The data presented in Table 1 is clear and unambiguous. The ethical challenges posed by the proposed 2-step research approach have been comprehensively unpacked.

	The following minor issues should be addressed: 1. Although implied, it might be useful to stress that the term "dose" encompasses a number of elements in the recommended posology - the quantum of the dose(s) for different patient populations, frequency and duration, but also the route of administration (and hence the dosage form marketed). The latter consideration can be particularly important in terms of feasibility of use, especially in resource-constrained settings. 2. Although the challenges of applying a 2-step development approach to the initial investigation of repurposed or novel drugs is covered, are there specific concerns about future research in the context of existing, proven treatments or in relation to the development of adapted or multi-valent vaccines? How might the proposed approach be applied in a context where placebo-controlled studies are no longer considered ethical? 3. In the examples provided of vaccine dosing (in the text and Table), it may be useful to include the international non-proprietary names, where those have been allocated (elasomeran, tozinameran). 4. Pg 9, line 29 - spelling of "myocarditis" 5. Pg 11, line 17 - the first sentence of the Conclusion appears to be a fragment: "Maximizing the benefits generated by limited drug supplies due to a scarcity of information." 6. A number of the references have been inaccurately captured in the bibliographic software used (#1,4,7,14,16,19,20,21).

VERSION 1 – AUTHOR RESPONSE

Reviewer Comments

Reviewer: 1: Dr. Laura Matrajt, Fred Hutchinson Cancer Research Center Vaccine and Infectious Disease Division

R1: Comments to the Author:
In the manuscript entitled “Dose Optimization and Scarce Resource Allocation: Two sides of the same coin”, Strohbehn et al. discuss the use of dose optimization during a pandemic as a way to stretch the available supply of a scarce resource (a vaccine for example).
The manuscript is well written and the points made are clear and well documented. My only comments are:
1) the manuscript can be strengthen if the authors add to their manuscript the fact that mathematical models of fractional dosing (for COVID and for other infectious diseases like cholera or flu) have shown that providing a lower dose (with potentially a lower efficacy) to more people can indeed be the optimal use of resources when the goal is to minimize overall deaths or infections. However, caution needs to be taken as there is a threshold in the efficacy: if lowering the dose reduces the efficacy too much, then fractional dosing becomes ineffective.

AU: We appreciate the Reviewer’s comment and have updated the manuscript to include mentions of mathematical modeling evidence from other, non-COVID-19, disease states, including yellow fever, flu, and cholera (page 10, lines 4-17).

R1: 2) I also suggest the authors add this citation
https://www.nature.com/articles/s41591-021-01440-4
As this paper has already dealt with this problem before.
AU: We appreciate the Reviewer’s comment; it was indeed an oversight on our part not to have included a citation to Dr Cowling’s work in the first draft.

Competing interests of Reviewer: NA

Reviewer: 2: Mr. Andy L Gray, University of Kwazulu-Natal
R2: Comments to the Author:
The authors have presented a thought-provoking and well-reasoned commentary, highlighting a critical issue from a novel perspective. The data presented in Table 1 is clear and unambiguous. The ethical challenges posed by the proposed 2-step research approach have been comprehensively unpacked.

AU: We appreciate the Reviewer's comment.

R2: The following minor issues should be addressed:
1. Although implied, it might be useful to stress that the term "dose" encompasses a number of elements in the recommended posology - the quantum of the dose(s) for different patient populations, frequency and duration, but also the route of administration (and hence the dosage form marketed). The latter consideration can be particularly important in terms of feasibility of use, especially in resource-constrained settings.

AU: We appreciate the Reviewer's comment and agree wholeheartedly. We have included an additional brief paragraph stating as much and stressing that our work focuses on the quantum. Insofar as efficacy is a function of exposure, we think it extremely important to, in the interests of health service efficiency, identify the extent to which quantum and frequency impact efficacy. We choose to expound upon these two due to the heavy focus on vaccines but acknowledge that the other factors listed have a role to play in other applications. We include this as a new section (page 11, line 32 through page 12, line 19).

R2: 2. Although the challenges of applying a 2-step development approach to the initial investigation of repurposed or novel drugs is covered, are there specific concerns about future research in the context of existing, proven treatments or in relation to the development of adapted or multi-valent vaccines? How might the proposed approach be applied in a context where placebo-controlled studies are no longer considered ethical?

AU: We appreciate the Reviewer's comment. Indeed, we agree that once a clinical trial has demonstrated the efficacy of a given drug (i.e., proven the principle that a given drug is efficacious), it is not ethical to conduct a placebo-controlled study. One approach in this setting would be to conduct a randomized, dose-ranging study that allows for subjects in the lower-dose arms to crossover to the standard-dose upon failure.

R2: 3. In the examples provided of vaccine dosing (in the text and Table), it may be useful to include the international non-proprietary names, where those have been allocated (elasomeran, tozinameran).

AU: We appreciate the Reviewer's comment and have made the appropriate modifications.

R2: 4. Pg 9, line 29 - spelling of "myocarditis"

AU: We appreciate the Reviewer's attention to detail and have updated the spelling.

R2: 5. Pg 11, line 17 - the first sentence of the Conclusion appears to be a fragment: "Maximizing the benefits generated by limited drug supplies due to a scarcity of information."

AU: We appreciate the Reviewer's attention to detail and have updated the relevant sentence.

R2: 6. A number of the references have been inaccurately captured in the bibliographic software used (#1,4,7,14,16,19,20,21).

AU: We appreciate the Reviewer's attention to detail and have updated the references.

Competing interests of Reviewer: I have no specific conflicts of interest. I serve on the South African

National Essential Medicines List Ministerial Advisory Committee on COVID-19 Therapeutics as well as three advisory committees at the South African Health Products Regulatory Authority.

VERSION 2 – REVIEW

REVIEWER	Matrajt, Laura Fred Hutchinson Cancer Research Center Vaccine and Infectious Disease Division
REVIEW RETURNED	09-Sep-2022

GENERAL COMMENTS	Refs 46 and 47 are the same.

REVIEWER	Gray, Andy L University of Kwazulu-Natal, Discipline of Pharmaceutical Sciences
REVIEW RETURNED	09-Sep-2022

GENERAL COMMENTS	The authors have comprehensively addressed each of the issues raised in the initial review. The manuscript is acceptable for publication without further review or revision.